Support for amended Claims 50, 69, 91 and 128-131 is found throughout the specification and in the originally filed claims. No new matter has been introduced.

The remainder of this Reply is set forth under appropriate subheadings for the convenience of the Examiner.

Claim rejection under 35 U.S.C. § 132

The Examiner rejected the phrase "having saturated acyl chains" in Claims 50, 69 and 91 as new matter on the grounds that the passage referred to by Applicants did not contain this phrase and, therefore, this phrase is not supported by the original disclosure.

Applicants respectfully disagree. However, Claims 50, 69, 91 and 128-131 have been amended to remove the phrase "having saturated acyl chains." Thus, it is not necessary to determine the complex issue of new matter here. Withdrawal of the rejection is respectfully requested.

The Examiner also rejected the phrase "having a solute concentration of less than 1 weight/volume percent" in Claims 50, 69 and 91 as new matter on the grounds that the passage referred to by Applicants did not contain this phrase and, therefore, this phrase is not supported by the original disclosure.

Applicants respectfully disagree. However, Claims 50, 69, 91 and 128-131 have been amended to remove the phrase "having a solute concentration of less than 1 weight/volume percent." Thus, it is not necessary to determine the complex issue of new matter here. Withdrawal of the rejection is respectfully requested.

Claim rejection under 35 U.S.C. § 103(a)

Claims 50-69, 91-108 and 128-131 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Durrani *et al.* (Durrani).

In support of the rejection the Examiner states:

> One of ordinary skill in the art would have been motivated to make a spray dried composition of a drug and a lipid based on the generic claim of Durrani. The expected result would be a stable spray dried powder formulation. Therefore, this invention as a

whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully traverse this rejection. Applicants respectfully submit that Claims 50-69, 91-108 and 128-131, as amended, are directed to subject matter not embraced by the teachings of the cited reference. In addition to the arguments previously made, which are incorporated by reference herein in their entirety, Applicants would like to emphasize that the present invention teaches methods for producing particles having properties and formulations neither disclosed nor suggested by Durrani.

According to MPEP §2142, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of skill in the art, to modify the reference or to combine the teachings of the reference to teach the invention. Second, there must be a reasonable expectation of success in practicing the invention. Finally, the prior art reference must teach or suggest all the claim limitations. Durrani fails on all three criteria.

The present invention, as claimed, is directed to methods of producing protein containing particles in which the protein has improved stability. The particular problems associated with protein stability in aqueous solutions are described in the instant application. For example, the spray drying of proteins can result in materials that are thermally degraded upon processing. Morever, there can be the detrimental effect of protein degradation at the air-liquid interface of the droplets in the spray. Applicants' teach that the problems associated with protein stability can be solved by producing the protein particles according to the methods of the invention.

In contrast, Durrani is not concerned with, and does not address, the stability of any drug in any resulting spray-dried powder from Durrani's method. Even if it could be inferred that Durrani addresses the stability of the drug, Durrani does not address the stability of a protein drug in a resulting spray-dried powder. Durrani is not about a method for producing spray-dried particles comprising a stabilized protein or peptide wherein the particles consist essentially of the stabilized protein, or peptide, the phospholipid and, optionally, the buffer salt; and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

Rather, Durrani is concerned with preparing drug/lipid powders effective to form liposomes with high drug encapsulation upon rehydration of the dried powder particles (See page

4, lines 11-15). Therefore, the generic claim of Durrani provides no suggestion or motivation for the ordinarily skilled artisan to select the specific components of Applicants' particles to produce particles with improved stability of a protein. Given that Durrani contains no specific examples directed to particles containing proteins, the ordinarily skilled artisan does not have a reasonable expectation of success of producing protein particles with improved stability based on the generic claim of Durrani. In addition, Durrani does not teach or suggest compositions containing the specific components as contained in the present claims.

Durrani describes an improved method for direct spray-drying a drug/lipid composition to produce a powder which forms liposomes upon rehydration that is essentially equivalent to that achieved by previous methods of spray-drying a drug/lipid compositions which required the ***preformation*** of a liposome encapsulated drug suspension prior to spray-drying the liposome encapsulated drug suspension. Durrani teaches that the improved method alleviates the prior art need to ***preform*** liposome encapsulated drug suspensions while producing equivalent powders, and goes on to describe the ingredients and steps required to produce such powders. Durrani is silent regarding the stability of any drug in the resulting powders. Durrani is only concerned about generating a powder which, upon rehydration, yields liposome encapsulated drug at a comparable percent encapsulation to spray-dried preformed liposomes. Therefore, there is no motivation or suggestion to use the methods of Durrani to overcome the obstacles involved with the spray-drying of proteins or which would direct the ordinarily skilled artisan to modify the cited generic claim to reach Applicants' claimed invention.

Durrani also fails to provide the ordinarily skilled artisan with a reasonable expectation of success in practicing the claimed methods directed to methods of producing particles with improved protein stability. As discussed above, Durrani does not address any of the issues associated with protein stability, but rather describes a method of producing liposomes which is stated as having applicability to a range of therapeutics. The only working examples in Durrani teach particles which include, not a protein (or a peptide), but rather albuterol sulfate. Durrani never addresses the issue of protein stability, but rather, Durrani limits his teachings to a method for achieving the liposomal encapsulation of a drug. Moreover, these working examples all contain components such as EPG and cholesterol which, while useful in producing liposomes, are not utilized in Applicants' methods. Therefore, the ordinarily skilled artisan searching for a

method to produce particles with improved protein stability would not be provided a reasonable expectation of success in practicing the claimed methods by the teachings contained in the cited generic claim of Durrani.

Finally, Durrani fails to teach or suggest all the claim limitations of Applicants methods. Claims 50-69, 91-108 and 128-131, as amended, are directed to a method for producing spray-dried particles having improved stability of a protein or peptide comprising combining a protein or peptide, a phospholipid and, optionally, a buffer salt and a co-solvent or an organic solvent, and spray drying the resulting mixture to produce spray-dried particles comprising a stabilized protein or peptide wherein the particles consist essentially of the stabilized protein, or peptide, the phospholipid and, optionally, the buffer salt; and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent. In Claims 128-131 the buffer salt is required. More importantly, Durrani specifically states that "the aqueous solution be free of phosphate salts" page 11, line 15. The particles of the instant invention have no such restriction and can be prepared using phosphate salts (see Example 2). Accordingly, the properties of the Durrani particles which necessitate that the aqueous solution be "phosphate free" simply do not exist in the particles of the instant invention. Thus, Durrani teaches away from the instant invention.

Durrani is interested in a method for preparing a powder which, upon rehydration, yields liposome encapsulated drug at a comparable percent encapsulation to spray-dried preformed liposomes. As such Durrani does not focus on nor address the special problems arising with protein stability when spray drying. Furthermore, all working examples presented in Durrani specifically teach particles which include, in addition to albuterol sulfate and lipid(s), other ingredients such as α- tocopherol, cholesterol and freon. Applicants note, for instance, the presence of the additional ingredient α-tocopherol, which at page 9, lines 20-21 is described as "a drug-protective and lipid-protective agent," in all formulations taught with specificity in the working examples of Durrani. Accordingly, Durrani teaches away from particles which do not need such ingredients as a "drug-protective and lipid-protective agent" as taught by Durrani.

Thus, Durrani includes in its particles additional ingredients which materially affect the basic and novel characteristics of the claimed invention. Applicants respectfully submit that Durrani does not teach, suggest or recognize the possibility of preparing spray dried particles

comprising a stabilized protein (or peptide) which consists essentially of the protein, phospholipid and, optionally, the buffer salt of the present claims.

As such, the claimed invention is non-obvious over the Durrani reference. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

50. (Twice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid [having saturated acyl chains], a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture [having a solute concentration of less than 1 weight/volume percent]; and

(b) spray-drying said mixture to produce spray-dried particles [having improved stability of the] comprising a stabilized protein;

wherein the particles consist essentially of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

69. (Twice Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid [having saturated acyl chains], a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture [having a solute concentration of less than 1 weight/volume percent]; and

(b) spray-drying said mixture to produce spray-dried particles [having improved stability of the] comprising a stabilized peptide;

wherein the particles consist essentially of the stabilized peptide, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

91. (Twice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid [having saturated acyl chains], an organic solvent, and, optionally, a buffer salt, to form a mixture [having a solute concentration of less than 1 weight/volume percent]; and

(b) spray-drying said mixture to produce spray-dried particles [having improved stability of the] comprising a stabilized protein;

wherein the particles consist essentially of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

128. (Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid [having saturated acyl chains], a buffer salt and a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles [having improved stability of the] comprising a stabilized protein;

wherein the particles consist essentially of the stabilized protein, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

129. (Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid [having saturated acyl chains], a buffer salt and a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles [having improved stability of the] comprising a stabilized peptide;

wherein the particles consist essentially of the stabilized peptide, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

130. (Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid [having saturated acyl chains], a buffer salt and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles [having improved stability of the] comprising a stabilized protein;

wherein the particles consist essentially of the stabilized protein, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

131. (Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid [having saturated acyl chains], a buffer salt and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles [having improved stability of the] comprising a stabilized peptide;

wherein the particles consist essentially of the stabilized peptide, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.